DEVICE FOR THE DETERMINATION OF BLOOD CLOTTING BY CAPACITANCE OR RESISTANCE

A microsystem for determining clotting time of blood and a low-cost, single-use device for use therein are provided wherein the device has no moving parts or expensive optical sensors or magnets. The device includes a microfluidic channel and a microsensor at least partially in fluid communication with the channel. By analyzing changes in the sensor as a drop of blood flows down the microfluidic channel, the time at which the blood clots can be determined.


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DEVICE FOR THE DETERMINATION OF BLOOD CLOTTING BY CAPACITANCE OR RESISTANCE

This application claims the benefit of U.S. provisional application Serial No. 60/434,186, filed December 17, 2002 and entitled “Microsystem for Clotting Time Blood Tests.”

BACKGROUND OF THE INVENTION

1. Field of the Invention

This application relates to microsystems for determining clotting time of blood and low-cost, single-use devices for use therein.

2. Background Art

The following references are referred to herein:


In an effort to reduce health care costs, the medical industry has been moving away from centralized laboratories to point-of-care instrumentation and analysis. One such example is near-patient blood coagulation analyzers [1], including Technidyne Corp.'s Hemachron 8000 and Cardiovascular Dynamics Inc.'s TAS. Many different diseases, including Hemophilia A and B, thrombocytopenia, Christmas disease, and prothrombin deficiency, affect the in vivo coagulation of blood. Treatment of these diseases requires medication with either coagulants or anticoagulants like the industry standard heparin or tamin [2,3]. In order to ensure proper medication, at-home testing would be a great benefit for individuals suffering from these diseases. Near-patient blood testing during cardiac surgery is equally important because blood clotting must be monitored to ensure a successful operation. An accelerated clotting time (ACT) test is used in this situation to make sure the patient is properly heparinized [4].

Clearly there is a need for low-cost blood coagulation analyzers. Additionally, disposable, single-use devices are preferable so as to avoid autoclaving and other cleaning procedures.

Blood coagulation analysis is useful for determining proper medication for medical conditions such as hemophilia, liver disease, and cardiac surgeries and has many uses in laboratories, hospitals, and even at home.

The following is a brief list of some makers of blood coagulation analyzers, the product name, and the detection scheme:

1. Helena Laboratories (http://www.helena.com) makes an instrument called the Actalyke. This device places a magnet in the blood and oscillates it back and forth detecting the rate of movement. The change in rate of movement detects coagulation.

2. i-STAT (http://www.istat.com) makes an instrument called the i-STAT. This device uses an indicator substance to detect hemocrit. This indicator is then sensed electrochemically.
3. Instrumentation Laboratories (http://www.ilus.com) makes an instrument called the GEM PCL. This device flows the blood past an optical window until the blood no longer passes indicating that it has clotted.

4. International Technidyne Corporation (http://www.itcmed.com) makes an instrument called the ProTime Microcoagulation System. This is intended to be an at-home test device. The coagulation is detected by pumping a precise amount of blood back and forth in a channel until it no longer flows.

5. Sienco, Inc. (http://www.uscid.org/~sienco/) has an instrument called Sonoclot. Sonoclot works by placing a mechanical probe into the blood and mechanically resonating it back and forth. By detecting the resistance to motion changes, a determination of the blood's coagulation can be determined.

The following are prior art U.S. patents related to blood clot sensors:

U.S. Patent No. 5,039,617 – McDonald et al describes capillary channels in plastic devices for measuring accelerated clotting time tests. Included in this patent are chambers for mixing the reagents needed for the ACT tests and methods for including the reagents. Optical or electromechanical techniques are used for detection of coagulation times.

U.S. Patent No. 6,521,182 – Shartle et al. A channel flow to a measurement area where optical transmittance is measured. A disposable cartridge-type device.

U.S. Patent No. 5,504,011 – Gavin et al. A channel-type device that requires pneumatic pumps to move fluid back and forth, thus recording its clotting time.
U.S. Patent No. 5,908,786 – Moreno et al. A long elongated channel with microheaters underneath. A thermonic compound is mixed with the blood and based on how far it flows into the channel, the color is changed and the results are read by the users like a litmus paper test.

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U.S. Patent No. 6,448,024 is an update of the McDonald et al. patent. The device is used to measure both clotting time and amount of fibrinogen by mixing in different compounds.

U.S. Patent No. 4,797,369 – Mintz. Blood is continuously brought together in a chamber and then separated. A fibrigen bridge is formed between the two solutions when clotting starts and this creates an electrical short between the two solutions.

10 Published U.S. Patent Application No. 0180824 – Mpock. Mechanical components spin in the solution and periodically raise out of the blood. Clots form on the spinning arms and are detected optically.


U.S. Patent No. 4,125,327 – Margolis. Plunger-type device that can add compounds into whatever solution one is measuring. Reaction changes are measured optically.

20 U.S. Patent No. 4,876,069 – Jochimsen. Metal stirrer or ball in the blood that creates turbidity. Clotting time is measured by measuring turbidity optically.

U.S. Patent No. 4,964,728 – Kloth et al. Describes similar mechanisms to U.S. Patent No. 4,876,069.

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U.S. Patent No. 5,167,145 – Butler et al. Uses infrared to measure composition changes in the blood as it clots.

U.S. Patent No. 6,555,064 – Baugh et al. Benchtop device that sends a plunger into a test-tube with blood in it. Clotting is measured by the rate of descent of the plunger.

U.S. Patent No. 6,438,498 – Opalsky et al., Measures chemical composition of the clots as they flow across a channel. Uses conductivity and amperometric sensors to measure composition.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a microsystem for determining clotting time of blood and a low-cost, single-use device for use therein wherein the device has no moving parts or expensive optical sensors or magnets.

In carrying out the above object and other objects of the present invention, a microsystem for determining clotting time of blood is provided. The microsystem includes a single-use device including: a microfluidic channel formed in the device; inlet and outlet ports in fluid communication with the channel wherein the inlet port allows the introduction of blood into the channel and wherein the blood flows along a length of the channel; and a microsensor at least partially in fluid communication with the channel for sensing a property of the blood at various locations along the length of the channel and providing corresponding signals. The microsystem also includes a signal processor which processes the signals to obtain the clotting time.

The signal processor may include a circuit for processing the signals to obtain a stop signal which indicates that the blood is clotted.

Further in carrying out the above object and other objects of the present invention, a low-cost, single-use device for analyzing blood coagulation is
provided. The device includes a microfluidic channel. Inlet and outlet ports are in fluid communication with the channel. The inlet port allows the introduction of blood into the channel, and the blood flows along a length of the channel. A microsensor is at least partially in fluid communication with the channel for sensing a property of the blood at various locations along the length of the channel and providing corresponding signals.

The microsensor may include a pair of spaced, conductive traces extending along the length of the channel.

The conductive traces may be equally spaced or variably spaced along the length of the channel.

At least one of the conductive traces may be segmented at predetermined intervals along the length of the channel.

The conductive traces may be conductive metal or carbon traces.

The channel may be spiral-shaped to minimize footprint size of the device.

The microsensor may be spiral-shaped or may be spoke-shaped.

The property of the blood may be at least one of impedance and capacitance of the blood in the channel.

The conductive traces may include Ag/AgCl, gold, platinum or iridium lines at least partially disposed in the channel.

The microsensor may include a set of spaced conductors disposed in the channel adjacent the inlet port to provide a start signal when the blood is first introduced into the channel.
The device may further include a substrate and a cap including the inlet port. The channel is disposed between the cap and the substrate.

The blood may flow in the channel by either capillary action or laminar flow.

The above object and other objects, features, and advantages of the present invention are readily apparent from the following detailed description of the best mode for carrying out the invention when taken in connection with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURES 1a-1d are side, sectional schematic views illustrating a typical microchannel processing sequence; Figure 1a shows a starting substrate; Figure 1b shows Ag sputtering and patterning with liftoff; Figure 1c shows spinning and patterning of SU-8; Figure 1d shows bonding of a glass cap and etching of openings to the channel;

FIGURE 2 is a schematic perspective view of a unit-length of a portion of a microchannel with a pair of spaced conductive traces of the present invention;

FIGURE 3 is a top, sectional schematic view showing the lay out of a spiral-shaped microchannel of the present invention;

FIGURES 4a and 4b are perspective, schematic views (Figure 4b being an enlarged view of a portion of Figure 4a) of a layout of the spiral-shaped microchannel;

FIGURE 5 is a side, sectional schematic view illustrating pressure differential in a laminar flow fluid;
FIGURE 6 is a 3D graph showing length of blood flow at a typical clotting time vs. channel width and height;

FIGURE 7 is a graph of length of non-clotting blood (i.e., non-coagulating blood flow) vs. time;

FIGURE 8 is a graph of viscosity vs. time which illustrates a piecewise linear approximation of viscosity;

FIGURE 9 is a graph of length of clotting blood (i.e., coagulating blood flow) vs. time;

FIGURE 10 is a graph of resistance of blood vs. time;

FIGURE 11 is a schematic view of interface electronics for stop signal generation;

FIGURE 12 is a graph of stop signal vs. time for clotting and non-clotting blood; and

FIGURES 13a-13h are schematic views of various electrode configurations wherein Figures 13g and 13h also show two possible microchannel configurations.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

A microsystem and an inexpensive, disposable device for use in the microsystem capable of performing blood clotting tests at a patient's home or bedside are provided. The device generally includes a microchannel and a detection sensor. A small amount of blood is dispensed into the channel where capillary action and pressure differentials cause the blood to flow down the length of the channel. As clotting occurs, the blood will stop flowing and a determination that the blood has stopped traveling down the channel can be made by the sensor. The
sensor can be, but is not limited to, an impedance sensor, a capacitance sensor, or a digital switch readout. The stop time is recorded and by taking the difference between the start time and stop time of the test, the clotting time of the blood can be determined.

The device may be fabricated by any number of techniques including, but not limited to, thin-film processing, injection molding, or lamination technologies.

**Microfluidic Channel**

As discussed above, the microfluidic channel can be fabricated in any number of cost-effective ways. One method of fabrication using thin-film processing techniques is discussed as an example. Figures 1a-1d are diagrams of the processing steps involved in forming the device. First, a suitable substrate 10 is chosen (this can be silicon with oxide or other passivation films, glass, etc.), and the sensing metal 12 is patterned onto the substrate 10. Next, a channel 13 is formed using a photoset polymer 14 such as SU-8 or polyimide films. Finally, a glass cap 16 (or other suitable material) is attached to the top of the channel 13 and an inlet hole 18 and an outlet hole (shown at 20 in Figure 3) are etched or drilled in the cap 16 to allow the blood into the channel 13. Figure 2 shows a unit-length cross-section of the microchannel 13 with the spaced conductive or metal traces 12 therein.

An example layout of the channel 13 is shown in Figure 3. The channel 13 was laid out in a spiral to minimize the footprint size, but other configurations can be used if other design parameters are desired. Figures 4a and 4b show a 3D perspective of the channel 13 as drawn in a MEMCAD.

**Sensor**

Sensing the distance that the blood has traveled down the channel 13 can be achieved by a number of techniques. By placing the two parallel metal traces
12 throughout the length of the channel 13 (Figures 2 and 13a), a resistive or capacitive readout can be taken depending on the metal chosen. For example, if the blood has traveled a distance \( L(t) \), then the resistance seen between the two metal traces \( R(t) \) is:

\[
R(t) = \frac{\rho}{z} \frac{w}{L(t)}
\]  

(1)

where \( \rho \) is the resistivity of blood, \( w \) is the separation between the metal lines 12, and \( z \) is the height of the channel 13. To increase the sensitivity of the device, the metal traces 12 can start some distance \( d \) into the channel 13 so that the effective distance traveled \( L_{\text{eff}}(t) \) becomes \( L(t) - d \) and the impedance is given by:

\[
R(t) = \frac{\rho}{z} \frac{w}{(L(t) - d)}
\]  

(2)

Another sensor example is a digital switch readout. Multiple pairs of traces (i.e., Figure 13d) of metal can be placed at intervals throughout the length of the channel 13. As the blood flows past a certain metal trace pair, it will effectively "close the switch" indicating that the blood has reached that location. The switches can then be read out as a thermometer code indicating the distance the blood has traveled.

By monitoring the rate of change of resistance or capacitance, the clotting time can be determined. Similarly, by setting some conditions on the rate that consecutive digital switches must close, a clotting time can be determined with the digital switch technique. The timebase can be as simple as an operator with a stopwatch waiting for an indication from the device to stop the counter, or as complex as an integrated timing circuit with counters and digital readout detailing the clotting time.

It should also be noted that this device can incorporate other sensors into the channel 13 that might give useful information about the blood. For
instance, ion-selective electrodes and voltammetric and temperature sensors could be added with only minimal changes to the device.

**Microfluidic Channel**

The following description is based on laminar flow rather than capillary flow. The blood may flow in the channel by either capillary action or laminar flow.

As the blood begins to flow down the channel 13, it exhibits laminar flow characteristics (Figure 5) and is governed by Laplace’s Law:

\[ \Delta P = P_2 - P_1 = \frac{4 \sigma}{d_{cir}} \]  

(3)

where \( P \) is the pressure, \( \sigma \) is the surface tension of the blood and \( d_{cir} \) is the cross-sectional area of the channel 13 if it were a circular rather than rectangular channel and is given by:

\[ d_{cir} = \frac{4 \times \pi \times \ell}{2 \times (x + z)} \]  

(4)

By conservation of mass,

\[ L(t)A = Q(L,t)t \]  

(5)

where \( L(t) \) is the length the blood has flowed in time \( t \), \( A \) is the cross-sectional area of the channel, and \( Q(L,t) \) is the volume flow rate of a liquid as a function of length and time. Poiseuille’s Flow equation states that:

\[ Q(L,t) = \frac{\pi \cdot \Delta P \cdot (d_{cir}/2)^4}{8 \cdot \eta(t) \cdot L(t)} \]  

(6)
where $\eta(t)$ is the viscosity of the blood versus time. Differentiating (5) yields:

$$A \frac{\partial L}{\partial t} = Q(L, t) + t \frac{\partial Q(L, t)}{\partial t}$$

and further substitution yields,

$$\left(\frac{16A}{\pi \Delta P(d_{circ}/2)^4}\right) L \frac{\partial L}{\partial t} = \left(\frac{1}{\eta} - t \frac{\partial \eta}{\partial t}\right) \frac{\partial t}{\partial t}$$

Thus, for a constant, worst-case low viscosity, which indicates that the blood does not coagulate,

$$L(t) = \frac{\pi \Delta P(d_{circ}/2)^4 t}{4 \cdot A \eta}$$

where $\eta(t)$ has been replaced by a constant viscosity, $\eta$. Equation (9) gives the maximum length of the blood in the channel 13 at any time.

Figure 6 is a plot of the length the blood travels down the channel as given by (9) at a typical clotting time versus channel dimensions. The plot shows various $(x,z)$ pairs that yield a minimum channel length and thus, minimize die area and fabrication costs. Based on this information, the width, $x$, was chosen to be 50 $\mu$m to minimize layout area yet still be wide enough to let blood flow unimpeded. The corresponding height, $z$, is 450 $\mu$m, and the necessary channel length is 100 mm.

Figure 7 shows a plot of blood flow for non-coagulating blood vs. time for these values of $x$ and $z$. The data is plotted through 300 seconds which is four times as long as will typically be needed for a clotting test.
Determining the length of the blood flow during coagulation requires that the time-dependent viscosity be used in (7). To simplify the integration of the differential equation, a piecewise linear approximation of the changing viscosity was used (Figure 8). The formula is:

\[
\eta(t) = \begin{cases} 
800 & \text{for } t < 72s \\ 
38.8t - 1906 & \text{for } t \geq 72s 
\end{cases}
\]  

Thus, solving (9) yields,

\[
L(t) = C_1 \sqrt{\int_0^t \left( \frac{1}{\eta(t)} - \frac{t}{\eta^2 \frac{\partial \eta}{\partial t}} \right) \, dt} \text{ or}
\]

\[
L(t) = \begin{cases} 
C_1 \sqrt{\int_0^{t/72} \frac{1}{800} \, dt} & \text{for } t \leq 72s \\ 
C_1 \sqrt{\int_0^{72} \frac{1}{800} \, dt + \int_{72}^{t} \frac{1906}{38.8t - 1906^2} \, dt} & \text{for } t > 72s 
\end{cases}
\]  

where \( C_1 \) is constant.

The plot of blood flow during coagulation versus time is shown in Figure 9. By comparing Figure 7 and Figure 9, it can be seen that the clotting blood travels a significantly shorter distance than the non-coagulating blood.

**Sensor Example (Impedance)**

Normally, a double-layer capacitance exists between a metal electrode and an ionic solution such as blood forming a polarized interface [10]. Ag/AgCl, in contrast, has the ability to exchange ions with the solution forming an ohmic connection between the electrode and the solution. The clotting time is measured by examining the varying resistance between the Ag/AgCl lines (spaced 30 \( \mu \text{m} \) apart, for example in Figure 2) on the channel floor as the blood travels down the
channel 13. However, it is to be understood that gold, platinum or iridium lines would be most likely used for capacitive readout. Also, carbon or other conductive materials could be used.

Like the surface tension of blood, the conductivity changes with respect to time as it clots [11], but this changing conductivity occurs after blood flow has stopped. Thus, a standard value for resistivity of blood, $\rho = 150 \, \Omega/cm$ [12], was used in these calculations.

The value of resistance at a time, $t$, is given by:

$$ R(t) = \frac{\rho}{\varepsilon} \frac{w}{L(t)} $$

(13)

This, however, yields a very small $\Delta R$ when the distance of the blood flow is greater than 60 mm. Since this is the distance of blood flow for a typical clotting time test, the Ag/AgCl lines 12 that measure the impedance are started 40 mm away from the opening where the blood is initially dispensed. Thus, the resistance becomes,

$$ R(t) = \frac{\rho}{\varepsilon} \frac{w}{(L(t) - 0.04)} $$

(14)

The data generated by (14) for both clotting, and non-clotting blood is presented in Figure 10. From the plot, the resistance seen across the blood at the nominal clotting distance is around 4 $\Omega$. A second set of Ag/AgCl lines 12 are placed directly under the blood inlet. These lines 12 give an instantaneous change in resistance as the blood is first injected to indicate the ACT test has started.

Figure 11 shows an example readout circuit that can measure impedance. However, it is to be understood that any number of different circuit topologies could be used. When the blood is first inserted into the channel 13, a start signal is generated. Once the blood flow has traveled 40 mm into the channel 13, the resistance, $R_{\text{blood}}$, begins to change as shown in Figure 10. This changes the voltage at the input of the amplifier, Amp1. The feedback configuration around Amp1 has a bandpass response set by the two capacitors, C1 and C2, and the diode
connected transistors, M1-M4 [13]. Thus, Amp1 only has gain while $R_{\text{blood}}$ is changing. This gain drives the output of the comparator, Amp2, to a logic high. When $R_{\text{blood}}$ stops changing because the blood has clotted, the output of the amplifier will go to zero volts and the comparator output will go to a logic low. The low-frequency pole of the bandpass response enables detection of slow changing impedances but does not pass any DC impedance values. Thus, the output bit is driven low when the rate of change of resistance drops below a certain level. This indicates that clotting has occurred, and the clotting time can be calculated as the time difference between the positive edge of the start signal and the negative edge of the stop signal.

The readout circuitry was simulated using SPECTRE by Cadence Designs. SPECTRE, through its Analog-HDL interface, allowed the programming of the resistor, $R_{\text{blood}}$, to mimic the resistance changes as blood flowed down the channel according to Figure 10. Figure 12 shows the output of the readout circuitry for both clotting and non-clotting blood.

Figures 13a-13h show a number of possible electrode configurations for the microsensor. The different electrode configurations can be intermixed or combined.

Figure 13a shows two parallel electrodes which could traverse the length of the channel 13. The distance blood flows is measured through an analog impedance change.

Figure 13b shows two sets of parallel electrodes down the length of the channel. The first set acts as a digital “start” bit when blood first hits them, immediately shorting them out electrically.

Figure 13c shows multiple sections of parallel electrodes used to measure the analog impedance change with greater resolution.
Figure 13d shows many short electrodes which are electrically shorted together when the blood reaches them. Data is read out digitally like watching switches close.

Figure 13e shows one continuous reference electrode to reduce pin count. The other electrodes can be read digitally or by an analog impedance method. This method can be extended to all of the electrode configurations presented herein.

Figure 13f shows that the electrodes can have changing separations to help increase the resolution of the impedance measurement at long blood flow distances.

At this point, it is important to note that readout can use resistance, capacitance, or combination measurements.

Figure 13g shows that the electrodes 12 can intersect the channel 13. This creates step-size resistance changes.

Figure 13h shows that the electrodes 12 can form a kind of spoke design with the spiral channel 13. The electrodes 12 can be in pairs or they can share a common “reference” electrode.

While embodiments of the invention have been illustrated and described, it is not intended that these embodiments illustrate and describe all possible forms of the invention. Rather, the words used in the specification are words of description rather than limitation, and it is understood that various changes may be made without departing from the spirit and scope of the invention.
WHAT IS CLAIMED IS:

1. A microsystem for determining clotting time of blood, the microsystem comprising:
   a single-use device including: a microfluidic channel formed in the device; inlet and outlet ports in fluid communication with the channel wherein the inlet port allows the introduction of blood into the channel and wherein the blood flows along a length of the channel; and a microsensor at least partially in fluid communication with the channel for sensing a property of the blood at various locations along the length of the channel and providing corresponding signals; and
   a signal processor for processing the signals to obtain the clotting time.

2. The microsystem as claimed in claim 1, wherein the microsensor includes a pair of spaced, conductive traces extending along the length of the channel.

3. The microsystem as claimed in claim 2, wherein the conductive traces are equally spaced along the length of the channel.

4. The microsystem as claimed in claim 2, wherein the conductive traces are variably spaced along the length of the channel.

5. The microsystem as claimed in claim 2, wherein at least one of the conductive traces is segmented at predetermined intervals along the length of the channel.

6. The microsystem as claimed in claim 2, wherein the conductive traces are conductive metal or carbon traces.

7. The microsystem as claimed in claim 1, wherein the channel is spiral-shaped to minimize footprint size of the device.
8. The microsystem as claimed in claim 7, wherein the microsensor is also spiral-shaped.

9. The microsystem as claimed in claim 7, wherein the microsensor is spoke-shaped.

10. The microsystem as claimed in claim 1 wherein the signal processor includes a circuit for processing the signals to obtain a stop signal which indicates that the blood is clotted.

11. The microsystem as claimed in claim 1, wherein the property of the blood is at least one of impedance and capacitance of the blood in the channel.

12. The microsystem as claimed in claim 2, wherein the conductive traces includes Ag/AgCl, gold, platinum or iridium lines at least partially disposed in the channel.

13. The microsystem as claimed in claim 1, wherein the microsensor includes a set of spaced conductors disposed in the channel adjacent the inlet port to provide a start signal when the blood is first introduced into the channel and wherein the signal processor processes the start signal.

14. The microsystem as claimed in claim 1, wherein the device further includes a substrate and a cap having the inlet port, the channel being disposed between the cap and the substrate.

15. A low-cost, single-use device for analyzing blood coagulation, the device comprising:

   a microfluidic channel;
   inlet and outlet ports in fluid communication with the channel wherein the inlet port allows the introduction of blood into the channel and wherein the blood flows along a length of the channel; and
a microsensor at least partially in fluid communication with the channel for sensing a property of the blood at various locations along the length of the channel and providing corresponding signals.

16. The device as claimed in claim 15, wherein the microsensor includes a pair of spaced, conductive traces extending along the length of the channel.

17. The device as claimed in claim 16, wherein the conductive traces are equally spaced along the length of the channel.

18. The device as claimed in claim 16, wherein the conductive traces are variably spaced along the length of the channel.

19. The device as claimed in claim 16, wherein at least one of the conductive traces is segmented at predetermined intervals along the length of the channel.

20. The device as claimed in claim 16, wherein the conductive traces are conductive metal or carbon traces.

21. The device as claimed in claim 15, wherein the channel is spiral-shaped to minimize footprint size of the device.

22. The device as claimed in claim 21, wherein the microsensor is also spiral-shaped.

23. The device as claimed in claim 21, wherein the microsensor is spoke-shaped.

24. The device as claimed in claim 15, wherein the property of the blood is at least one of impedance and capacitance of the blood in the channel.
25. The device as claimed in claim 16, wherein the conductive traces includes Ag/AgCl, gold, platinum or iridium lines at least partially disposed in the channel.

26. The device as claimed in claim 15, wherein the microsensor includes a set of spaced conductors disposed in the channel adjacent the inlet port to provide a start signal when the blood is first introduced into the channel.

27. The device as claimed in claim 15, further comprising a substrate and a cap including the inlet port, the channel being disposed between the cap and the substrate.

28. The microsystem as claimed in claim 1, wherein the blood flows in the channel by capillary action or laminar flow.

29. The device as claimed in claim 15, wherein the blood flows in the channel by capillary action or laminar flow.
Fig. 11

Fig. 12
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

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<th>G01N33/49</th>
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According to international Patent Classification (IPC) or to both national classification and IPC.

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, INSPEC, PAJ, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Patent family members are listed in annex.

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Date of the actual completion of the international search

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Date of mailing of the international search report

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Form PCT/05/A210 (second sheet) (January 2004)
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